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Title: **Combination of a pde iv inhibitor and a**

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Abstract: The subject invention relates to therapeutic combinations and me inflammatory conditions and diseases. Particularly the present inv methods for PDE IV-related conditions and for TNF-alpha-related PDE IV inhibitor and a TNF-alpha antagonist.

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Claims:

1. A method for the treatment or prophylaxis of a PDE IV- or a TNF-alpha-related such treatment or prophylaxis comprising administrating to the mammal an amou amount of a TNF-alpha antagonist wherein the amount of the PDE IV inhibitor an antagonist together comprise a therapy effective for the treatment or prophylaxis condition.

2. The method of claim 1, wherein the TNF-alpha antagonist is selected from the metalloproteinase inhibitor, a tetracycline TNF-alpha antagonist, a fluoroquinolon quinolone TNF-alpha antagonist.

3. The method of claim 1, wherein the PDE IV inhibitor is selected from the group ZK-117137, bamifylline, dyphylline, ibudilast, and theophylline.

4. The method of claim 1, wherein the PDE IV inhibitor is selected from the group IV inhibitor, a xanthine PDE IV inhibitor, and a benzamide PDE IV inhibitor.

5. The method of claim 4, wherein the PDE IV inhibitor is selected from the group dichloropyridin-4-yl)-3-ethyl-1H-indazole-6-carboxam- ide, 1-cyclopentyl-3-ethyl hexahydro-7H-p- yrazolo[3,4-c]pyridin-7-one, N-(4-oxo-1-phenyl-3,4,6,7-tetrahy yl)-1- H-indole-2-carboxamide, CI-1118, 4-[4-cyclopropyl-6-(cyclopropylamino)-: .about.,4-thiazinane-1,1-diol, and N-cyclopropyl-4-(2-methylcyclopropyl)-6-(2-m amine, atizoram, filaminast, piclamilast, tibenelast, CDP 840, GW 3600, NCS 613 000, SKF 107806, XT-44, tolafentrine, zardaverine,T-2585, SDZ-ISQ-844, SB 20: 4021, GF-248, IPL-4088, CP-353164, CP-146523, CP-293321, T-611,WAY-12612 093, CDC-801, CC-7085, CDC-998, CH-3697, CH-3442, CH-2874, CH-4139, RPR- 422, CH-673, CH-928, KW-4490, Org 20241, Org 30029,VMX 554, VMX 565, ben 17597, Nitraquazone, oxagrelate, T-440.

6. The method of claim 2, wherein the TNF-alpha antagonist is a TNF-alpha antib

7. The method of claim 6, wherein the TNF-alpha antibody is selected from the gr etanercept, CytoFAb, AGT-1, afelimomab, PassTNF, and CDP-870.

8. The method of claim 2, wherein the TNF-alpha antagonist is selected from the Onercept, Pegsunercept, interferon-gamma, interleukin-1, pentoxyphylline, pimol nitrogen oxide, napthopyridine, a lazaroid, hydrazine sulfate, ketotifen, tenidap, a thorazine, an antioxidant, a cannabinoid, glycyrrhizin, sho-saiko-to, and L-camitir

9. A therapeutic composition comprising an amount of a PDE IV inhibitor and an a a pharmaceutically acceptable excipient.

10. The therapeutic composition of claim 9, wherein the PDE IV inhibitor is select roflumilast, cilomilast, ZK- 117137, bamifylline, dyphylline, ibudilast, and theophy

11. The therapeutic composition of claim 9, wherein the PDE IV inhibitor is select catechol ether PDE IV inhibitor, a quinazolinedione PDE IV inhibitor, a xanthine PI IV inhibitor.

12. The therapeutic composition of claim 11, wherein the PDE IV inhibitor is selec cyclopentyl-N-(3,5-dichloropyridin-4-yl)-3-ethyl-1H-indazole-6-carboxam- ide, 1 methylphenyl)-1,3a,4,5,6,7a-hexahydro-7H-- pyrazolo[3,4-c]pyridin-7-one, N-(4 diazepino[6,7,1-hi]indol-3-yl)-1- H-indole-2-carboxamide, CI-1118, 4-[4-cyclopr triazin-2-yl]-llambda.about.4- .about.,4-thiazinane-1,1-diol, and N-cyclopropyl-4- methylmorpholin-4-yl)-1,3,5-tr- iazin-2-amine, atizoram, filaminast, piclamilast, 613, PDB 093, Ro 20-1724, RS 25344-000, SKF 107806, XT-44, tolafentrine, zar 207499, RPR-117658A, L-787258, E-4021, GF-248, IPL-4088, CP-353164, CP-14 126120, WAY-122331,WAY-127093B, PDB-093, CDC-801, CC-7085, CDC-998, CI RPR-114597, RPR-122818, KF-19514, CH422, CH-673, CH-928, KW-4490, Org 2(benafentrine, trequinsin, EMD 54622, RS 17597, Nitraquazone, oxagrelate, T-44C

13. The therapeutic composition of claim 9, wherein the TNF-alpha antagonist is a

14. The therapeutic composition of claim 13, wherein the TNF-alpha antibody is s infliximab, etanercept, CytoFAb, AGT-1, afelimomab, PassTNF, and CDP-870.

15. A kit for the purpose of treatment or prophylaxis of a PDE IV- or a TNF-alpha- need of such treatment or prophylaxis, the kit comprising a dosage form comprisi form comprising a TNF-alpha antagonist.

Description:

BACKGROUND OF THE INVENTION

[0001] 1. Field of the Invention

[0002] This invention relates to therapeutic combinations and methods for the tre and diseases. Particularly the present invention relates to treatments and methoc for TNF-alpha-related conditions.

[0003] 2. Description of Related Art

[0004] Tumor necrosis factor-alpha (TNF-alpha) is a proinflammatory cytokine ar immunological events. The major sources of TNF-alpha are mast cells, eosinphils, alpha causes a broad spectrum of effects both in vitro and in vivo, including vasc inflammation, activation of macrophages and neutrophils, leukocytosis, apoptosis associated with a variety of disease states including various forms of cancer, arth sepsis, autoimmune diseases, infarctions, obesity, asthma, COPD, cachexia, strok and uveitis.

[0005] TNF-alpha activity can be reduced by treatment with, for example, an ant antibodies include, individually, etanercept or infliximab. An alternative therapy u includes treating the patient with a glucocorticoid. Further individual therapies for are described by K. J. Tracey et al., Annu. Rev. Med. 45: 491-503 1994.

[0006] The enzyme phosphodiesterase-IV (PDE IV), is believed to be the predom within inflammatory cells. One of the primary activities of PDE IV is to metabolize signal transduction molecule cyclic adenosine 3',5'-monophosphate (cAMP).

[0007] The molecule cAMP is a ubiquitous second messenger produced in cells in and several neurotransmitters. The synthesis and release of proinflammatory me alpha) and active oxygen species are inhibited where there is an increased level c 35: 463-480, 2000).

[0008] In contrast, native PDE IV activity causes reduction of intracellular cAMP a release of several inflammatory cellular mediators including histamine and severa symptoms of inflammation. Chemical inhibition of PDE IV activity has been found cAMP, which in turn, down-regulate the harmful activity of inflammatory cells.

[0009] Multiple isoforms of the phosphodiesterase enzyme have been identified tl kinetic properties, responsiveness to endogenous regulators (Ca2+/calmodulin, c inhibition by various compounds. Phosphodiesterase isoforms include the phosph present invention, the preferred PDE isoform to be inhibited, is the cAMP-specific category of the PDE IV isoform, there are 4 known subtypes. The PDE IV subtype cyclic AMP, but differ in terms of their mRNA splicing and upstream conserved do are included within the scope of the term, "PDE IV", for purposes of the present i

[0010] PDE inhibitors like theophylline and pentoxyphylline inhibit all or most PDI tissue. These compounds exhibit side effects, apparently because they nonselecti classes in a variety of tissues. The target disease may be effectively treated by s secondary side effects may be exhibited which, if they could be avoided or minim therapeutic effect of this approach to treating certain diseases. See PCT publicatic compounds that inhibit multiple isoforms, in addition to PDE IV, of the PDE enzy ibudilast, benafentrine zardaverine, and pentoxyfyllin.

[0011] The therapeutic use a of PDE IV inhibitor with a PDE III inhibitor is descrit 00/66123. A method of treatment using a PDE IV inhibitor and a corticosteroid is WO 01/32127 A2.

[0012] Asthma affects about 10 million Americans, about a third of whom are un States alone billions of dollars are spent annually on asthma-related health care. characterizes asthma is brought about by a combination of three primary factors variable and reversible airway obstruction due to airway muscle contraction, 2) in 3) bronchial hyper-responsiveness that results in excessive mucus in the airways. among individuals, but common triggers include allergens such as dust mites and agents, and physical exertion or exercise.

[0013] The Mayo Clinic reports that chronic obstructive pulmonary disease (COPI bronchitis, kills 85,000 people a year in the United States. Chronic obstructive pu collectively to several chronic or progressive pulmonary diseases including asthm normal airflow), chronic obstructive bronchitis, bullous disease, and emphysema, example, chronic bronchitis involves an inflammation and eventual scarring of the producing symptoms including chronic cough, increase of mucus, frequent clearin breath. Emphysema results from the normal but chronic inflammatory response c to environmental pollutants such as cigarette smoke.

[0014] Drug treatment for asthma and COPD includes intravenous, oral, subcutar

bronchodilators including beta-adrenergics, methyl xanthines, and anti-cholinergi corticosteroids, the mast cell mediator-release inhibitors known as Cromolyn and leukotrienes, for anti-inflammatory effects. However, the cellular and molecular n immune processes that play a role in the pathogenesis and progression of asthma understood.

SUMMARY OF THE INVENTION

[0015] Briefly, therefore, the present invention is directed to a method for the tre a TNF-alpha-related condition in a mammal in need of such treatment or prophyl mammal an amount of a PDE IV inhibitor and an amount of a TNF-alpha antagoni inhibitor and the amount of the TNF-alpha antagonist together comprise an effect prevention of a PDE IV- or a TNF-alpha-related condition.

[0016] The invention is further directed to a therapeutic composition comprising an amount of a TNF-alpha antagonist and a pharmaceutically acceptable excipien

[0017] Another embodiment of the present invention provides a kit for the purpo PDE IV- or a TNF-alpha-related condition in a mammal in need of such treatment dosage form comprising a PDE IV inhibitor and a dosage form comprising a TNF-a

[0018] Further scope of the applicability of the present invention will become app provided below. However, it should be understood that the following detailed des preferred embodiments of the invention, are given by way of illustration only sinc within the spirit and scope of the invention will become apparent to those skilled i description.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0019] The following detailed description is provided to aid those skilled in the art Even so, this detailed description should not be construed to unduly limit the pres variations in the embodiments discussed herein can be made by those of ordinary the spirit or scope of the present inventive discovery.

[0020] The contents of each of the references cited herein, including the contents primary references, are herein incorporated by reference in their entirety.

a. Definitions

[0021] The following definitions are provided in order to aid the reader in underst present invention:

[0022] The term "asthma" refers to a respiratory disorder characterized by episo by any one or a combination of three primary factors including: 1) bronchospasm obstruction due to airway muscle contraction, 2) inflammation of the airway lining responsiveness resulting in excessive mucus in the airways, which may be trigger combination of allergens such as dust mites and mold, viral or bacterial infection cold" virus, environmental pollutants such as chemical fumes or smoke, physical stress, or inhalation of cold air. The terms "chronic obstructive pulmonary disease interchangeably herein refers to a chronic disorder or combination of disorders ch maximal expiratory flow and slow forced emptying of the lungs that does not cha and is not, or is only minimally, reversible with traditional bronchodilators. Comm chronic bronchitis, i.e. the presence of cough and sputum for more than three mo and emphysema, i.e. alveolar damage. However, COPD can involve singly or in co normal airflow, chronic bronchitis with airway obstruction (chronic obstructive bro bronchitis, or bullous disease.

[0023] The term "respiratory disease or condition" refers to any one of several ai affect a component of the respiratory system including especially the trachea, bro include without limitation asthmatic conditions such as allergen-induced asthma, induced asthma, cold-induced asthma, stress-induced asthma and viral-induced-a diseases including chronic bronchitis with normal airflow, chronic bronchitis with a bronchitis), emphysema, asthmatic bronchitis, or bullous disease. The term "resp include without limitation other pulmonary diseases involving inflammation includ disease, farmer's lung, acute respiratory distress syndrome, pneumonia, aspiratic the lung, acidosis inflammation of the lung, acute pulmonary edema, acute moun

acute pulmonary hypertension, persistent pulmonary hypertension of the newbor hyaline membrane disease, acute pulmonary thromboembolism, heparin-protamii asthmaticus and hypoxia.

[0024] The terms "phosphodiestrease inhibitor" and "PDE inhibitor" as used inter that reduces the physiological effect of a phosphodisterase enzyme, for example : (cAMP) or cyclic (cGMP).

[0025] The term "PDE IV inhibitor" denotes a compound that is capable of reduci PDE IV isoform of phosphodiesterase.

[0026] A PDE IV inhibitor may show different in vitro IC.sub.50 values with respe vitro IC.sub.50 value exhibited by a compound for the inhibition of another isofor the IC.sub.50 value for the inhibition of PDE IVis referred to herein as "inter-isofo other PDE isoform.

[0027] The term "inter-isoform selective PDE IV inhibitor" refers to a PDE IV inhit selectivity with respect to another PDE isoform is greater than one.

[0028] It is believed that there are at least two binding forms on human monocyt IV) at which inhibitors bind. One explanation for these observations is that huma One binds rolipram with high affinity while the other binds rolipram with low affin by referring to them as the high affmity rolipram binding form (HPDE IV) and the has been reported that certain compounds which potently compete for HPDE IV h side effects than those which more potently compete with LPDE IV (see, for exam incorporated by reference). Further data indicate that compounds can be targetec PDE IV and that this form is distinct from the binding form for which rolipram is a interact with LPDE IV are reported to have anti-inflammatory activity, whereas th produce side effects or exhibit more intensely those side effects. Rolipram binds t high affinity (HPDE IV), defined herein as having a K.sub.i less than 10 nanomola affinity (LPDE IV), defined here as having a K.sub.i of greater than 100 nanomola method of measuring the in vitro IC.sub.50 ratios for a compound with respect to

[0029] As used herein, the term "intra-isoform selectivity" with respect to a parti IC.sub.50 with respect to HPDE IV divided by its in vitro IC.sub.50 with respect tc

[0030] The term "intra-isoform selective PDE IV inhibitor" means a PDE IV inhibit selectivity is about 0.1 or greater.

[0031] The terms "selective phosphodiesterase IV inhibitor" and "selective PDE IV exhibits either an inter-isoform selective PDE IV inhibitor or an intra-isoform sele

[0032] The term "subject" as used herein refers to an animal, in one embodiment embodiment particularly a human being, who is the object of treatment, observat embodiment the mammal can be, for example, a companion animal such as a do

[0033] The terms "dosing" and "treatment" as used herein refer to any process, a wherein a subject, particularly a human being, is rendered medical aid with the o condition, either directly or indirectly.

[0034] The term "therapeutic compound" as used herein refers to a compound us a disease or condition.

[0035] The term "therapeutically effective" as used herein refers to a characterist compound, or a characteristic of amounts of combined therapeutic compounds in combined amounts achieve the goal of preventing, avoiding, reducing or eliminati condition.

[0036] "Combination therapy" means the administration of two or more therapeu administration encompasses co-administration of these therapeutic agents in a su such as in a single capsule having a fixed ratio of active ingredients or in multiple ingredient. In addition, such administration also encompasses use of each type of manner. In either case, the treatment regimen will provide beneficial effects of th condition.

[0037] The term "pharmaceutically-acceptable salt" embraces salts commonly us

form addition salts of free acids or free bases. The nature of the salt is not critical acceptable or compatible with a medical therapy. Pharmaceutically acceptable sal of the methods of the present invention because of their greater aqueous solubilit or neutral compound. Such salts must have a pharmaceutically acceptable anion acceptable acid addition salts of compounds of the present invention may be prep organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hyc phosphoric acid. Appropriate organic acids include from aliphatic, cycloaliphatic, a carboxylic and sulfonic classes of organic acids, examples of which are formic, ac gluconic, lactic, malic, tartaric, citric, ascorbic, glucoronic, maleic, fumaric, pyruvi anthranilic, mesylic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic ethylsulfonic, benzenesulfonic, sulfanilic, stearic, cyclohexylaminosulfonic, algenic pharmaceutically-acceptable base addition salts of compounds of the present inve aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic s dibenzylethyleneldiamine, choline, chloroprocaine, diethanolamine, ethylenediami and procaine. Suitable pharmnaceutically acceptable acid addition salts of the cor when possible include those derived from inorganic acids, such as hydrochloric, h fluoroboric, phosphoric, metaphosphoric, nitric, carbonic (including carbonate anc sulfonic, and sulfuric acids, and organic acids such as acetic, benzenesulfonic, ber gluconic, glycolic, isothionic, lactic, lactobionic, maleic, malic, methanesulfonic, tr toluenesulfonic, tartaric, and trifluoroacetic acids. The chloride salt is particularly Suitable pharmaceutically acceptable base salts include ammonium salts, alkali m potassium salts, and alkaline earth salts such as magnesium and calcium salts. Al conventional means from the corresponding conjugate base or conjugate acid of t invention by reacting, respectively, the appropriate acid or base with the conjuga compound.

b. Detailed Description

[0038] In accordance with the present invention, there is now provided a method PDE IV- or a TNF-alpha-related condition in a mammal in need of such treatment administrating to the mammal an amount of a PDE IV inhibitor and an amount of amount of the PDE IV inhibitor and the amount of the TNF-alpha antagonist toget the treatment or prevention of a PDE IV- or a TNF-alpha-related condition. Prefer PDE IV inhibitor.

[0039] For purposes of the present invention, the terms "PDE IV inhibitor" refer t inhibit the PDE IV enzyme or which is discovered to act as a PDE IV inhibitor (PDE include any compound that is known or can be discovered to inhibit the PDE IV er compound also demonstrates inhibition of other isoforms of the phosphodiesteras

[0040] It is preferred that the PDE IV inhibitor that is used in the present inventic inhibitor.

[0041] To determine the inter-isoform selectivity of a PDE IV inhibitor, the putati incubated together with each individual isoform of phosphodiesterase and simulta nucleotides. PDE inhibition is then determined by the presence or absence of subs Hatzelmann, A., et al., J. Pharm. Exper. Therap., 297(1):267-279 (2001). The rel to slow or prevent the degradation of tritiated cyclic nucleotides is one test that is in question selects one or more of each isoform to inhibit. Representative PDE iso substrates can be obtained by isolation from appropriate tissues and their purcha

[0042] In practice, the in vitro selectivity of a PDE IV inhibitor may vary dependir test is performed and on the inhibitors being tested. However, for the purposes o PDE IV inhibitor can be measured as a ratio of the in vitro IC.sub.50 value for inh phosphodiesterase enzyme (Z) other than PDE IV, divided by the IC.sub.50 value IC.sub.50/PDE IV IC.sub.50), where Z identifies any PDE other than PDE IV. As u refers to the concentration of a compound that is required to produce 50% inhibit PDE IV selective inhibitor is any inhibitor for which the ratio of PDE Z IC.sub.50to a preferred embodiment, this ratio is greater than 2, more preferably greater thai 100, and more preferably still greater than 1000.

[0043] By way of example, in Hatzelmann, A., et al., J. Pharm. Exper. Therap., 2 for roflumilast activity on PDE IV was reported to be 0.0008 .mu.M, while the IC.s was reported to be >10 .mu.M. Accordingly, the selectivity of roflumilast for PDE >10/0.0008 or at least about 12,500. Likewise, the selectivity of roflumilast for P be 8/0.0008 or at least about 10,000.

[0044] Thus, preferred PDE IV selective inhibitors of the present invention have a 1 .mu.M, more preferred of less than about 0.1 .mu.M, even more preferred of le preferred still of less than about 0.001 .mu.M. Preferred PDE IV selective inhibitor than about 1 .mu.M, and more preferably of greater than 10 .mu.M.

[0045] An example of a selective PDE IV inhibitor that is particularly preferred for recently described for use in treating pulmonary inflammation is the pyridyl benza cyclopropylmethloxy-4-difluoromnethoxy-N-[3,5-dichloropyrid-4-yl]-benz- amide. PDE4 inhibitor. See U.S. Pat. No. 5,712,298, which in herein incorporated by refe

[0046] PDE IV inhibitors are classified into three main chemical classes 1) Catech variety of flexible molecules of inhibitors structurally related to rolipram) 2) Quina related to Nitraquazone and 3) Xanthines, to which theophylline belongs. Inside t distinguished quinazolindiones and xanthines.

[0047] Preferably the PDE IV inhibitor is selected from the group consisting of rol 117137, bamifylline, dyphylline, ibudilast, and Theophylline. Further individual PD invention are individually listed in Table 1. TABLE-US-00001 TABLE 1 No. Structu Reference 1. cilomilast Ariflo SB- 207499 CAS RN: 153259- 65-5 4-cyano-4-[3- c cyclohexane carboxylic acid Dal Piaz, V., et. al., Eur. J. Med. Chem. 35 (2000) 46 162401-32-3 3-(cyclopropylmethoxy)- N-(3,5-dichloropyridin- 4-yl)-4- (difluoron al., Immunopharmacology 47 (2000) 127-162 3. Pumafentrin BYK-33043 BY-343 8-methoxy- 2-methyl- 1,2,3,4,4a,10b- hexahydro-benzo [c][1,6] napthyridin-6- ' Norman P., Expert Opin. Ther. Patents (2002) 12(1):93-111 4. L-869298 CT-245 826141 Analogue: L- 791943 CT-5210 CAS RN: 225919-29-9 2-{4-[1-[3,4- bis(d oxidopyridin-4- yl)ethyl]phenyl]- 1,1,1,3,3,3- hexafluoropropan-2-ol Norman P., (1):93-111 5. ZK-117137 SH-636 Trade Name: Mesopram CAS RN: 189940-24-7 methyl-1,3-oxazolidin- 2-one US 2002/010310 6 A1 6. rolipram ME- 3167 ZK- 62 cyclopentyloxy- 4-methoxy-phenyl)- pyrrolidan-2-one Dal Piaz, V., et. al., Eur. J. YM-976 CAS RN: 191219- 80-4 4-(3-Chloro-phenyl)-1,7- diethyl-1H-pyrido[2,3- (A1 8. Sch-351591 D-4396 N-(3,5-dichloro-1- oxidopyridin-4-yl)-8- methoxy-2- (t carboxamide US 2002/010310 6 A1 9. IC-485 [1-benzyl-4-(1- cyclopentyl-3-ethy methylpyrrolidin-3- yl]methanol US 2002/010310 6 A1 10. D-4418 Sch- 365351 ' quinoline-5- carboxylic acid (2,5- dichloropyridin-3-yl) amide US 2002/010310 6 PD-168787 CI-1018 Analogue: PD-190749 Analogue: PD-190036 CAS RN: 19789 phenyl-1,2,4,5- tetrahydroazepino[3,2,1- hi]indol-5- yl]nicotinamide Dal Piaz, V., 463-480 12. CP-77059 CAS RN: 114918-24-0 3-(3-benzyl-2,4-dioxo- 3,4-dihydrc benzoic acid methyl ester Dal Piaz, V., et. al., Eur. J. Med. Chem. 35 (2000) 463- 75-4 8-(3-nitrophenyl)-6- (pyridin-4-ylmethyl) pyrido[2,3-d] pyridazin- 5(6H)-on Chem. 35 (2000) 463-480 14. AWD-12-281 Analogue: AWD-12-343 CAS RN: 25 yl)-2-[1-(4- fluorobenzyl)-5- hydroxy-1H-indol-3-yl]- 2-oxoacetamide US 2002/0 AWD-12-232 CAS RN: 182282-60-6 9-ethyl-2-methoxy-7- methyl-5- propylimida (5H)-one Dal Piaz, V., et. al., Eur. J. Med. Chem. 35 (2000) 463-480 16. YM-589 diethylpyrido[2,3- d]pyrimidin-2(1H)-one Dal Piaz, V., et. al., Eur. J. Med. Chem. CAS RN: 58-55-9 3,7-Dihydro-1,3- dimethyl-1H-purine-2,6- dione Dal Piaz, V., et 463-480 18. Cipamfylline HEP-688 BRL-61063 CAS RN: 132210-43-6 8-amino-1, purine-2,6- dione Dal Piaz, V., et. al., Eur. J. Med. Chem. 35 (2000) 463-480 19. 136145-07-8 3-(4-chlorophenyl)-1- propyl-3,7-dihydro-1H- purine-2,6-dione Dal 35 (2000) 463-480 20. V-11294A CAS RN: 162278-09-3 [3-(3-cyclopentyloxy-4- purin-6-yl]- ethyl amine hydrochloride Dal Piaz, V., et. al., Eur. J. Med. Chem. 35 Analogue: RPR-132703 N-(3,5- dimethylisoxazol-4-yl)- 4-methoxy-3- (tetrahydrc V., et. al., Eur. J. Med. Chem. 35 (2000) 463-480 22. IBMX CAS RN: 28822- 58-4 1H-purine-2,6- dione Dal Piaz, V., et. al., Eur. J. Med. Chem. 35 (2000) 463-480 7-isobutyl-1,3-dimethyl- 3,7-dihydro-1H-purine- 2,6-dione Dal Piaz, V., et. al., Eu 24. Doxofylline Trade Names: Ansimar Maxivent CAS RN: 69975-86-6 7-(1,3-dio dihydro-1H-purine- 2,6-dione Dal Piaz, V., et. al., Eur. J. Med. Chem. 35 (2000) 4 18-5 7-(2,3-dihydroxypropyl)- 1,3-dimethyl-3,7- dihydro-1H-purine-2,6- dione D 35 (2000) 463-480 26. Verofylline CAS RN: 65029-11-0 1,8-dimethyl-3-(2- meth dione Dal Piaz, V., et. al., Eur. J. Med. Chem. 35 (2000) 463-480 27. Bamifylline (hydroxy- methyl)amino]ethyl]-1,3- dimethyl-8-phenyl-3,7- dihydro-1H-purine-2 Med. Chem. 35 (2000) 463-480 28. Pentoxifylline CAS RN: 6493-05-6 3,7-dimeth purine-2,6-dione Dal Piaz, V., et. al., Eur. J. Med. Chem. 35 (2000) 463-480 29. I propyl-3,7-dihydro- 1H-purine-2,6-dione Dal Piaz, V., et. al., Eur. J. Med. Chem. CAS RN: 57076-71-8 1,3-dibutyl-7-(2- oxopropyl)-3,7-dihydro- 1H-purine-2,6-di Chem. 35 (2000) 463-480 31. Chiroscience 245412 3-(3-methoxyphenyl)-1- phe

Dal Piaz, V., et. al., Eur. J. Med. Chem. 35 (2000) 463-480 32. ICI 63197 CAS RN dihydro[1,2,4]triazolo[1,5- a][1,3,5]triazin-5(1H)- one Dal Piaz, V., et. al., Eur. J SCA 40 6-bromo-8- ethylimidazo[1,2- a]pyrazin-2-amine Dal Piaz, V., et. al., Eur 34. Ibudilast CAS RN: 50847-11-5 1-(2-isopropyl- pyrazolo[1,5- a]pyridin-3-yl)-2 al., Eur. J. Med. Chem. 35 (2000) 463-480 35. N-cyclopentyl- 8-cyclopropyl- 3-pr 162278-16-2 162278-06-0 N-cyclopentyl-8- cyclopropyl-3-propyl- 3H-purin-6-am Chem. 35 (2000) 463-480 36. 8-cyclopropyl- N,3-diethyl-3H- purin-6-amine CAS 126371-20-0 8-cyclopropyl-N,3- diethyl-3H-purin-6- amine Dal Piaz, V., et. al., E 37. INN: lirimilast BAY-19-8004 CAS RN: 329306-27-6 Methane suifonic acid 2-(benzofuran-6- yl ester Dal Piaz, V., et. al., Eur. J. Med. Chem. 35 (2000) 463-48(dihydroxybutyl)- 6-hydroxy-1- benzofuran-2- yl]methanone (4-chlorophenyl)[3-(benzofuran- 2-yl]methanone Dal Piaz, V., et. al., Eur. J. Med. Chem. 35 (2000) 4 [(dimethylamino)- methyl]-7-hydroxy- 5,6-dimethyl-1- benzofuran-2- yl}ethanor [(dimethylamino)methyl]- 7-hydroxy-5,6- dimethyl-1-benzofuran- 2-yl}ethanone Chem. 35 (2000) 463-480 40. N-(3,5- dichloropyridin-4- yl)-8-methoxy-2,2- dim (3,5-dichloropyridin- 4-yl)-8-methoxy-2,2- dimethylchromane-5- carboxamide Da 35 (2000) 463-480 41. 2-acetyl-N- benzyl-7- methoxy-1- benzofuran-4- sulfonar benzofuran- 4-sulfonamide Dal Piaz, V., et. al., Eur. J. Med. Chem. 35 (2000) 46: dichloro pyridin-4-yl)-3- ethyl-1H-indazole- 6-carboxamide 1-cyclopentyl-N-(3,5- indazole-6- carboxamide Dal Piaz, V., et. al., Eur. J. Med. Chem. 35 (2000) 463-4 methylphenyl)- 1,3a,4,5,6,7a- hexahydro-7H- pyrazolo[3,4- c]pyridin-7-one 1-cy methylphenyl)- 1,3a,4,5,6,7a- hexahydro-7H- pyrazolo[3,4-c]pyridin- one Dal Pia (2000) 463-480 44. N-(4-oxo-1- phenyl-3,4,6,7- tetrahydro[1,4]diazepino[6,7,1- carboxamide N-(4-oxo-1-phenyl- 3,4,6,7- tetrahydro[1,4]diazepino [6,7,1-hi]indo Piaz, V., et. al., Eur. J. Med. Chem. 35 (2000) 463-480 45. CI-1118 N-(9-methyl- [1,4]diazepino [6,7,1-hi]indol-3- yl)isonicotinamide Dal Piaz, V., et. al., Eur. J. M [4-(cyclopropyl-6- (cyclopropylamino)- 1,3,5-triazin-2-yl]- 1lambda.about.4.abou cyclopropyl-6- (cyclopropylamino)- 1,3,5-triazin-2-yl]- 1lambda.about.4.about.,4 al., Eur. J. Med. Chem. 35 (2000) 463-480 47. N-cyclopropyl-4-(2- methylcyclopr 1,3,5- triazin-2-amine N-cyclopropyl-4-(2- methylcyclopropyl)-6-(2- methylmorpl Piaz, V., et. al., Eur. J. Med. Chem. 35 (2000) 463-480 48. Atizoram CP 80633 C Pyrimidinone, 5- [3-[(1S,2S,4R)- bicyclo[2.2.1]hept-2- yloxy]-4-methoxyphenyl] Immunopharmacology 47 (2000) 127-162 49. Filaminast WAY-PDA-641 CAS RN: (cyclopentyloxy)-4- methoxyphenyl)-,O- (aminocarbonyl) oxime, (E) Souness, J., (2000) 127-162 50. Piclamilast RP 73401 RPR 73401 CAS RN: 144035-83-6 Benz dichloro-4-pyridinyl)-4- methoxy Dal Piaz, V., et. al., Eur. J. Med. Chem. 35 (200 186655 CAS RN: 105102-18-9 Sodium 5,6- diethoxybenzo(b)-thioph ene-2-carbo Immunopharmacology 47 (2000) 127-162 52. CDP 840 CAS RN: 162542-90-7 Py (cyclopentyloxy)-4- methoxyphenyl]-2- phenylethyl]- Souness, J., et al., Immunc GW 3600 GL 193600X CAS RN: 173258-94-1 1-Pyrrolidinecarboxylic acid, 3-acet methoxyphenyl]-3- methyl-, methyl ester, (3R,4R) US 2002/010310 6 A1 54. NC Purin-6-amine, 9- [(2-fluorophenyl)methyl]- N-methyl-2- (trifluoromethyl)- US 2(Structure US 2002/010310 CAS RN: 6 A1 444657-05-0 56. Ro 20-172 CAS RN: 2 butoxy-4- methoxyphenyl)methyl] US 2002/010310 6 A1 57. RS 25344- 000 CAS pyrimidine- 2,4(1H,3H)-dione, 1-(3- nitrophenyl)-3-(4- pyridinylmethyl) Dal Piaz, (2000) 463-480 58. SKF 107806 No Structure US 2002/010310 CAS RN: 6 A1 44

59. XT-44 CAS RN: 135462-05-4 1-n-butyl-3-n- propylxanthine Waki, Y., et al., J 60. tolafentrine Benzenesulfonamide, N-[4-[(4aR,10bS)- 1,2,3,4,4a,10b-hexahyd [1,6]- naphthyridin-6-yl]phenyl]- 4-methyl US 2002/010310 6 A1 61. zardaverin (difluoromethoxy)-3- methoxyphenyl] Souness, J., et al., Immunopharmacology (6,7-Diethoxy-2,3- bis-hydroxymethyl- napthalen-1-yl)-pyridin- 3-yl]-4-pyridin-3 with generic inorganic neutral component US 2002/010310 6 A1 63. SDZ-ISQ- 8 dimethoxy- 3,4-dihydro-isoquinolin- 3-yl]-methanol US 2002/010310 6 A1 64. SE cyclopentyloxy-4- methoxy-phenyl)- cyclohexylethynyl]- pyrimidin-2-ylamine Sou 47 (2000) 127-162 65. RPR- 117658A N-(3,5-Dichloro-1-oxy- pyridin-4-yl)-4-me ethoxy]-benzamide US 2002/010310 6 A1 66. L-787258 No structure US 2002/0 [1,3]dioxol- 5-ylmethyl)-amino]-6- chloro-quinazolin-2-yl}- piperidine-4-carboxy inorganic neutral component US 2002/010310 6 A1 68. GF-248 1-Methyl-5-[5-(2 phenyl]-3- propyl-1,4-dihydro- pyrazolo[4,3- d]pyrimidin-7-one US 2002/010310 2002/010310 6 A1 70. CP-353164 5-(3-Cyclopentyloxy-4- methoxy-phenyl)- pyri 2002/010310 6 A1 71. CP-146523 4'-Methoxy-3-methyl-3'- (5-phenyl-pentyloxy) 2002/010310 6 A1 72. CP-293321 No structure US 2002/010310 6 A1 73. XT-61 1,3,4,5a,8- pentaaza-as-indacen-5-one US 2002/010310 6 A1 74. WAY- No struc 75. WAY- 122331 1-(3-Cyclopentoxy-4- methoxy-phenyl)-7,8- dimethyl-3-oxa-1- 2002/010310 6 A1 76. WAY- 127093B 3-(3-Cyclopentyloxy-4- methoxy-phenyl)-

carboxylic acid (pyridin- 3-ylmethyl)-amide; compound with but-2- enedioic acid No structure US 2002/010310 6 A1 78. CDC-801 3-(3-Cyclopentyloxy-4- methox isoindol-2-yl)- propionamide US 2002/010310 6 A1 79. CC-7085 No structure US structure US 2002/010310 6 A1 81. CH-3697 No structure US 2002/010310 6 A1 2002/010310 6 A1 83. CH-2874 No structure US 2002/010310 6 A1 84. CH-4139 85. RPR- 114597 5-Methoxy-1-oxy-4- (tetrahydro-furan-3- yloxy)-pyridine-2- car pyridin-4- yl) amide US 2002/010310 6 A1 86. RPR- 122818 3-3(3,4-Dimethoxy- phenyl- heptanoic acid hydroxamide US 2002/010310 6 A1 87. KF-19514 5-Phen 1,3,5,6-tetraaza- cyclopenta[a]- naphthalene-A-one US 2002/010310 6 A1 88. Cl A1 89. CH-673 No structure US 2002/010310 6 A1 90. CH-928 No structure US 2 structure US 2002/010310 6 A1 92. Org 20241 4-(3,4-Dimethoxy- phenyl)-N-hyc 2002/010310 6 A1 93. Org 30029 N-Hydroxy-5,6- dimethoxy-benzo[b]- thiopene generic inorganic neutral component US 2002/010310 6 A1 94. VMX 554 No Stru Respiratory Diseases, 5.sup.th International Conference, San Diego, CA, USA, Jul Acetamide, N-[4- [(4aR,10bS)- 1,2,3,4,4a,10b-hexahydro- 8,9-dimethoxy-2- me phenyl] US 6,333,354 B1 96. Trequinsin 4H-Pyrimido[6,1- a]isoquinolin-4-one, 2, methyl-2- [(2,4,6-trimethyl- phenyl)imino] US 6,333,354 B1 97. EMD 54622 Quin oxo- 2H-1,3,4-thiadiazin-5-yl)- 1-(3,4-dimethoxybenzoyl)- 1,2,3,4-tetrahydro-4,4 17597 Pyrido[2,3-d]pyridazin- 5(6H)-one, 8-(3- nitrophenyl)-6-(4- pyridinylmeth Nitraquazone 2,4(1H,3H)- Quinazolinedione, 3- ethyl-1-(3-nitrophenyl) Dal Piaz, (2000) 463-480 100. Oxagrelate 6-Phthalazinecarboxylic acid, 3,4-dihydro-1- (hy ethyl ester US 6,333,354 B1

[0048] In one embodiment the PDE IV inhibitor is a catechol ether selected from roflumilast, pumafentrin, L-869298, ZK-117137, and rolipram. In a preferred eml cilomilast. In another preferred embodiment the PDE IV inhibitor is roflumilast. In PDE IV inhibitor is rolipram.

[0049] In another embodiment the PDE IV inhibitor is a quinazolidione or related consisting of YM-976, Sch-351591, IC-485, Sch-365351, PD-189659, CP-77059, and YM-58977.

[0050] In another embodiment the PDE IV inhibitor is a xanthine or related comp consisting of Theophylline, cipamfylline, arofylline, V-11294A, RPR-132294, IBMX verofylline, bamifylline, pentoxiylline, enprofylline, denbufylline, Chiroscience 245 cyclopentyl-8-cyclopropyl-3-propyl-3H-purin-6-amine, and 8-cyclopropyl-N,3-diet embodiment the PDE IV inhibitor is theophylline. In another preferred embodimer another preferred embodiment the PDE IV inhibitor is doxofylline. In another pref inhibitor is dyphylline. In another preferred embodiment the PDE IV inhibitor is ba embodiment the PDE IV inhibitor is ibudilast.

[0051] In another embodiment the PDE IV inhibitor is a benzofuran, benzopyran group consisting of lirimilast, (4-chlorophenyl)[3-(3,3-dihydroxybutyl)-6-hydroxy {3-(dimethylamino)-4-[(dimethylamino)methyl]-7-hydroxy-5,6-dimethy- l-1-ben dichloropyridin-4-yl)-8-methoxy-2,2-dimethylchromane-5-carboxamide- , and 2-a benzofuran-4-sulfonamide. In another embodiment the PDE IV inhibitor is selecte cyclopentyl-N-(3,5-dichloropyridin-4-yl)-3-ethyl-1H-indazole-6-carboxam- ide, 1- methylphenyl)-1,3a,4,5,6,7a-hexahydro-7H-p- yrazolo[3,4-c]pyridin-7-one, N-(4 diazepino[6,7,1-hi]indol-3-yl)-1- H-indole-2-carboxamide, CI-1118, 4-[4-cyclopr triazin-2-yl]-llambda.about.4- .about.,4-thiazinane-1,1-diol, N-cyclopropyl-4-(2-n methylmorpholin-4-yl)-1,3,5-tr- iazin-2-amine, and atizoram, filaminast, piclamil NCS 613, PDB 093, Ro 20-1724, RS 25344-000, SKF 107806, XT44, tolafentrine, SB 207499, RPR-117658A, L-787258, E-4021, GF-248, IPL-4088, CP-353164, CP 126120, WAY-122331, WAY-127093B, PDB-093, CDC-801, CC-7085, CDC-998, C 4139, RPR-114597, RPR-122818, KF-19514, CH-422, CH-673, CH-928, KW-4490 VMX 565, benafentrine, trequinsin, EMD 54622, RS 17597, Nitraquazone, oxagrel

[0052] In the present invention the TNF alpha anagonist is an agent, compound, containing an agent, compound or molecule, including analogs, isomers, homolog which antagonizes, inhibits, inactivates, reduces, suppresses, and/or limits the re cells of TNF alpha.

[0053] Preferably the TNF-alpha antagonist is selected from the group consisting metalloproteinase inhibitor, a corticosteroid, a tetracycline TNF-alpha antagonist, antagonist, and a quinolone TNF-alpha antagonist.

[0054] In one embodiment the TNF-alpha antagonist is a TNF-alpha antibody. Pre selected from the group consisting of infliximab, etanercept, CytoFAb, AGT-1, afe

[0055] In another embodiment the TNF-alpha antagonist is a metalloproteinase ii metalloproteinase inhibitor is a matrix metalloproteinase inhibitor.

[0056] In another embodiment the TNF-alpha antagonist is a corticosteroid. Prefe from the group consisting of mometasone, fluticasone, ciclesonide, budesonide, b deflazacort, betamethasone, methyl-prednisolone, dexamethasone, prednisolone, triamcinolone, cortisone, corticosterone, dihydroxycortisone, beclomethasone dipi

[0057] In another embodiment the TNF-alpha antagonist is a tetracycline TNF-alp tetracycline TNF-alpha antagonist is selected from the group. consisting of doxyc tetracycline, lymecycline, and 4-hydroxy-4-dimethylaminotetracycline.

[0058] In another embodiment the TNF-alpha antagonist is a fluoroquinolone TNF fluoroquinolone TNF-alpha antagonist is selected from the group consisting of nor lomefloxacin, gatifloxacin, perfloxacin, and temafloxacin.

[0059] In another embodiment the TNF-alpha antagonist is a quinolone TNF-alph TNF-alpha antagonist is selected from the group consisting of vesnarinone and an

[0060] In another embodiment the TNF-alpha antagonist is selected from the gro Onercept, Pegsunercept, interferon-gamma, interleukin-1, pentoxyphylline, pimol nitrogen oxide, napthopyridine, a lazaroid, hydrazine sulfate, ketotifen, tenidap, a thorazine, an antioxidant, a cannabinoid, glycyrrhizin, sho-saiko-to, and L-camitir

[0061] The present invention provides for a therapeutic composition for the treati TNF-alpha-related condition in a mammal in need of such treatment or prophylax mammal an amount of a PDE IV inhibitor and an amount of a TNF-alpha antagoni inhibitor and the amount of the TNF-alpha antagonist together comprise an effect IV- or a TNF-alpha-related condition.

[0062] The therapeutic composition of the present invention comprises an amour of a TNF alpha antagonist.

[0063] The present invention also provides for a kit for the purpose of treatment alpha-related condition in a mammal in need of such treatment or prophylaxis, th comprising a PDE IV inhibitor and a dosage form comprising a TNF-alpha antagon

Dosage Forms and Delivery System.

[0064] The PDE IV inhibitor, the TNF alpha antagonist, or pharmaceutical compos administered enterally and parenterally. Oral (intra-gastric) is a preferred route o useful in the present inventioncan be administered, for example, in solid dosage f invention, which include tablets, capsules, pills, and granules, which can be prepa enteric coatings and others well known in the art. Liquid dosage forms for oral ad acceptable emulsions, solutions, suspensions, syrups, and elixirs. Topical dosage invention include ointments, powders, sprays, inhalants, creams, jellies, collyrium

[0065] Parenteral administration includes subcutaneous, intramuscular, intradern other administrative methods known in the art. Enteral administration includes sc capsules, enteric coated capsules, and syrups. When administered, the pharmace body temperature.

[0066] Compositions intended for oral use may be prepared according to any met manufacture of pharmaceutical compositions and such compositions may contain group consisting of sweetening agents, flavoring agents, coloring agents and pres pharmaceutically elegant and palatable preparations. Tablets can contain the acti toxic pharmaceutically acceptable excipients which are suitable for the manufactu be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lac phosphate, granulating and disintegrating agents, for example, maize starch, or a example starch, gelatin or acacia, and lubricating agents, for example magnesiun tablets may be uncoated or they may be coated by known techniques to delay dis gastrointestinal tract and thereby provide a sustained action over a longer period such as glyceryl monostearate or glyceryl distearate may be employed.

[0067] Formulations for oral use may also be presented as hard gelatin capsules mixed with an inert solid diluent, for example, calcium carbonate, calcium phospl capsules wherein the active ingredients are present as such, or mixed with water peanut oil, liquid paraffm, or olive oil.

[0068] Aqueous suspensions can be produced that contain the active materials in the manufacture of aqueous suspensions. Such excipients include suspending age carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium tragacanth and gum acacia. Dispersing or wetting agents may be naturally-occurr lecithin, or condensation products of an alkylene oxide with fatty acids, for examp condensation products of ethylene oxide with long chain aliphatic alcohols, for ex or condensation products of ethylene oxide with partial esters derived from fatty polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate. polyethylene oxide (PEG).

[0069] The aqueous suspensions may also contain one or more preservatives, for hydroxybenzoate, one or more coloring agents, one or more flavoring agents, or as sucrose or saccharin.

[0070] Oily suspensions may be formulated by suspending the active ingredients oil, for example, arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil suspensions may contain a thickening agent, for example beeswax, hard paraffin

[0071] Sweetening agents, such as those set forth above, and flavoring agents m oral preparation. These compositions may be preserved by the addition of an anti

[0072] Dispersible powders and granules suitable for preparation of an aqueous s provide the active ingredient in admixture with a dispersing or wetting agent, a su preservatives. Suitable dispersing or wetting agents and suspending agents are e mentioned above. Additional excipients, for example sweetening, flavoring and co

[0073] Syrups and elixirs containing the PDE IV inhibitor and/or the TNF alpha an sweetening agents, for example glycerol, sorbitol, or sucrose. Such formulations preservative and flavoring and coloring agents.

[0074] The subject method of prescribing a PDE IV inhibitor and a TNF alpha anta parenterally, either subcutaneously, or intravenously, or intramuscularly, or intra the form of sterile injectable aqueous or olagenous suspensions. Such suspension known art using those suitable dispersing of wetting agents and suspending agen or other acceptable agents. The sterile injectable preparation may also be a steril non-toxic parenterally-acceptable diluent or solvent, for example as a solution in vehicles and solvents that may be employed are water, Ringer's solution and isot addition, sterile, fixed oils are conventionally employed as a solvent or suspendin fixed oil may be employed, including synthetic mono- or diglycerides. In addition, find use in the preparation of injectables.

[0075] Also, administration can be delivered by inhalation, whether oral or nasal of the present invention can include formulations as are well known in the art, tha delivery by inhalation. A metered dose inhaler or a nebulizer provides aerosol deli providing delivery of a range of particle sizes including particles in the preferred r microns. Particles larger than about 10 microns are deposited primarily in the mo smaller than about 0.5 microns are inhaled to the alveolae and then exhaled with An alternative device for inhalant therapy is a dry powder inhaler using, for exam carry the therapeutic compound. For all forms of inhalant therapy, factors other t also influence the amount of deposition in the lungs, including tidal volume, rate Therefore, an individual being instructed in inhalation therapy according to the m be instructed to take slow deep breaths and hold each breath for several seconds seconds. Typically, the total daily dose of the therapeutic compounds according t will be administered as 1-4 puffs on a b.i.d-q.i.d. basis (i.e. twice-a-day, three tir as needed, or solely on an as-needed basis.

PDE IV Inhibitor Dosage Amount

[0076] Daily dosages can vary within wide limits and will be adjusted to the indiv

case. In general, for administration to adults, an appropriate daily dosage has be limits that were identified as being preferred may be exceeded if expedient. The single dosage or in divided dosages. Various delivery systems include capsules, t example. TABLE-US-00002 TABLE 2 PDE IV Dosage Inhibitor Amount REFERENCE et al., Immunopharmacology, 47: 127-162 (2000) Rolipram 0.5-2 mg/kg per day Instituto Oswaldo Cruz, 92(II): 193-196 (1997); Souness, J., et al., Immunophar Arofylline 20 mg per day Souness, J., et al., Immunopharmacology, 47: 127-162 Souness, J., et al., Immunopharmacology, 47: 127-162 (2000) Tibenalast 150 m Immunopharmacology, 47: 127-162 (2000) Piclamilast 0.2-0.8 mg per day Soun 47: 127-162 (2000) CDP-840 30 mg per day Souness, J., et al., Immunopharma 2 mg/kg per day Teixeira, M., et al., Memorias do Instituto Oswaldo Cruz, 92(II): per day Trifilieff, A., et al., J. Pharmacol. Exp. Ther., 301(1): ABE171 241-248 (2

[0077] The exact dosage and regimen for administering a PDE IV inhibitor will ne and duration of action of the compounds used, the nature and severity of the illne age, weight, general health and individual responsiveness of the patient to be tre circumstances. While not intended to be limiting, an example of the normally pre inhibitor, roflumilast, has been reported to be about 0.5 mg once daily for human al., J. Allergy Clin. Immunol. 108(4):530-536 (2001). In humans, roflumilast has dosed at between about 0.01 and 0.5 mg/kg of body weight for inhalation and be body weight per day for systemic therapies. See U.S. Pat. No. 5,712,298.

[0078] Other examples of recommended PDE IV dosages are include in Table 2.

Table 2

[0079] Therefore, for purposes of the present invention, it is preferred to dose th sufficient to provide a steroid-sparing benefit when given as a combination thera treatment, wherein the amount of the PDE IV inhibitor which is administered and which is administered together comprise a therapeutically effective amount of the

[0080] More preferred is to dose the PDE IV inhibitor to a subject in need of such and 10 mg/kg of body weight per day. More preferred, the PDE IV inhibitor shoul about 0.01 and 5 mg/kg per day. Even more preferred still, the PDE IV inhibitor s between about 0.1 and 2.0 mg/kg per day.

TNF Alpha Antagonist Dosage Amount

[0081] Etanercept is known to those in the art. For adult patients the recommenc administered as a subcutaneous injection given twice a week at least 72-96 hour 2002. For pediatric patients ages 4-17 years, the recommended dose of etanerce 25 mg per dose) administered as a subcutaneous injection given twice a week at

[0082] Infliximab is know to those skilled in the art. The recommended dose of ir an intravenous infusion. Id. Infliximab is also administered in combination with m of infliximab in combination with methotrexate is 3 mg/kg administered as an int additional similar doses at 2 and 6 weeks after the first infusion then every 8 wee

[0083] Other examples of recommended TNF alpha antagonist dosages are incluc 3 TNF ALPHA ANTAGONIST DOSAGE AND ROUTE OF ADMINISTRATION Remicade as an intravenous infusion anti-tumor necrosis factor followed w/ additional simil monoclonal antibody after the first infusion and then every 8 weeks thereafter En as a subcutaneous (Etanercept) injection 72-96 hours apart. soluble TNF receptor 160 mg/day - suspension Doxycycline Oral & IV: 200 mg/day in adults on the firs 100 mg q 12 h for the entire course of therapy has also been used. In children 8 day, and thereafter 2 mg/kg/day; 4 mg/kg/day for the entire course has also bee mg followed by 100 mg q 12 h in adults and in children 8 yrs & older 4 mg/kg foll Oxytetracycline Oral: 250-500 mg q 6 h to adults and 25-50 mg/kg/day in childre h to adults and 10-25 mg/kg/day in children 8 yr & older. Tetracycline Oral: 250- mg/kg/day in children 8 yr & older. IV: 250-500 mg q 12 h to adults and 10-25 n Norfloxacin Oral: 400 mg bid Ofloxacin Oral & IV: 200-400 mg bid Ciprofloxacin C q 12 h. Gatifloxacin Oral: 200 mg & 400 mg tablets IV: 20 mL (200 mg) & 40 mL Loading dose: 40 mg IVP over 3 minutes (0.75 mg/kg) Maintenance dose: 250-9 Interferon-gamma Interferon gamma 1b (Actimmune) injection 100 mcg (2 Millio per day Pentoxyphylline Oral- Controlled Release 400 mg tid Melatonin Oral - 3-1 Desk Reference, 56.sup.th Edition, 2002.

Therapeutic Uses

[0084] The present invention encompasses the therapeutic treatment of several i example, the methods of the present invention are useful for the treatment of pu pulmonary hypertension, asthma, exercised induced asthma, pollution induced as osteoarthritis, adult respiratory distress syndrom, infant respiratory distress synd retinopathy, diabetic angiopathy, edema formation, arthritis, rheumatoid arthritis disease, chronic bronchitis, eosinophilic granuloma, psoriasis and other benign or endotoxic shock (and associated conditions such as laminitis and colic in horses), reperfusion injury of the myocardium and brain, osteoporosis, chronic glomerulor adult respiratory distress syndrome, infant respiratory distress syndrome, chronic diabetes insipidus, rhinitis (including allergic rhinitis), allergic conjunctivitis, verna atherosclerosis, neurogenic inflammation, pain, cough, ankylosing spondylitis, tra host disease, hypersecretion of gastric acid, bacterial, fungal or viral induced seps cytokine-mediated chronic tissue degeneration, cancer, cachexia, conjunctivitis, c depression, inflammatory bowel disease, allergic responses to insect and arthropc monopolar depression, acute and chronic neurodegenerative disorders with inflan disease, Alzheimer's disease, spinal cord trauma, head injury, joint injury, multipl cancerous invasion of normal tissues, including any other disorders that are amer inhibition of the PDE IV isoenzyme and the resulting elevated cAMP levels via adn such treatment of an effective amount of the compounds referred to in the methc

[0085] In view of the above, it will be seen that the several advantages of the inv advantageous results obtained.

[0086] As various changes could be made in the above methods and composition the invention, it is intended that all matter contained in the above description sha in a limiting sense.

c. Assays and Screens

Inhibition of PDE Isoenzymes

[0087] The assay mixture contains 50 mM Tris (pH 7.4), 5 mM MgCl.sub.2, 0.5 .r cAMP or [.sup.3H]cGMP (about 30,000 cpm/assay), the indicated concentration o enzyme solution at a final assay volume of 200 .mu.l.

[0088] Stock solutions of the compounds are diluted 1:100 (v/v) in the Tris buffe dilutions are prepared in 1% (v/v) DMSO/Tris buffer, which are diluted 1:2 (v/v) fmal concentrations of the inhibitors at a DMSO concentration of 0.5% (v/v). DMS activities.

[0089] After preincubation for 5 min at 37.degree. C., the reaction isstarted by th cGMP) and the assays are incubated for further 15 min at 37.degree. C. Then 50 reaction and the assays are left on ice for about 10 min. Following incubation with atrox snake venom) for 10 min at 37.degree. C., the assays areloaded on QAE Se Poly-Prep chromatography columns; Bio-Rad, Munchen, Germany). The columns ammonium formate (pH 6.0) and the eluate is counted for radioactivity. Results a (measured in the presence of denatured protein) that are below 5% of total radio nucleotides hydrolyzed does not exceed 30% of the original substrate concentrati

[0090] PDE1 from bovine brain is assayed in the presence of Ca.sup.2+ (1 mM) a as substrate. A blankvalue is measured in the presence of EGTA (1 mM) is subtra heart is chromatographically purified and is assayed in the presence of cGMP (5 .r and PDE5 are assayed in the cytosol of human platelets using cAMP and cGMP, re tested in the cytosol of human neutrophils using cAMP as substrate. The PDE3-sp is included to suppress PDE3 activity originating from contaminatingplatelets. See Exper. Therap., 297(1):267-279 (2001).

TNF.alpha. Assay

[0091] Cells areincubated in 96-well plates (Primaria 3872) at a density of 5.time volume of 200 .mu.l (RPMI 1640 medium containing 10% AB-serum for monocyte modified Dulbecco's medium containing 10% FBS for dendritic cells). Compounds stimulation of the cells with "LPS working solution" (10 .mu.l): a stock solution of

0.1% (v/v) hydroxylamine in PBS; after sonication for 5 min, 1-ml aliquots are st the experiment, this solution is fiwther diluted in the corresponding cell-specific c solution. The appropriate cell-specific submaximal final LPS concentrations are de and are 1 ng/ml for monocytes and 100 ng/ml for macrophages and dendritic cell PGE.sub.2 (10 nM) is added as a cAMP trigger to provideresponsiveness of the ce

[0092] Stock solutions of the compounds are diluted 1:50 (v/v) in medium; subs DMSO/medium to achieve the final drug concentrations in the assays at a DMSO itself does not affect TNF.alpha. synthesis. Starting from a 10 mM stock solution i in medium so that the resulting DMSO concentration at the final compound conce

[0093] After overnight culture (about 13 h) in the case of monocytes and macrop cells, supernatants (about 180 .mu.l) are removed and stored at -20.degree. C. t commercially available enzymimmunoassay from Immunotech (Hamburg, Germa the manufacturer's instructions. See Hatzelmann, A., et al., J. Pharm. Exper. The

Lung Function/Capacity

[0094] The degree and severity of asthma and COPD can be determined by meas expiratory flow rates. Measurement can accomplished with, for example, a spiron pneumotach, before and after each of the treatments. Use of spirometry is a stan of PDE IV inhibitors and corticosteroids after administration to a patient suffering disorder. A device called a spirometer is used to measure how much air the lungs system is able to move air into and out of the lungs.

[0095] Spirometry is a medical test that measures the physical volume of air an into a device. The objective of spirometry is to assess ventilatory function. An est which the volume is changing as a function of time can also be calculated with sp Measurement and Inteipretation of Ventilatory Function in Clinical Practice, Rob P Society of Australia and New Zealand (1995). Thus, with the methods of the pres comparisons of pulmonary airflow before and after treatment will elucidate simila of skill to determine the effectiveness of the treatment methods.

[0096] Common parameters that spirometry measures are Forced Vital Capacity measured in liters that can be forcibly and rapidly exhaled. Another parameter is volume of air expelled in the first second of a forced expiration. Normal paramete inflammatory disorder such as asthma or COPD is: Tidal volume--5 to 7 milliliters Expiratory reserve volume--25% of vital capacity; Inspiratory capacity--75% of v -75% of vital capacity after 1 second, 94% after 2 seconds, and 97% after 3 secc as a percentage, and are considered abnormal if less than 80% of the normal pre usually indicates the presence of some degree of obstructive lung disease such as restrictive lung disease such as pulmonary fibrosis or asthma.

EXAMPLE 1.

[0097] table of Preferred Combinations TABLE-US-00004 TABLE 4 Example Numt Inhibitor 1 arofylline & Infliximab 2 arofylline & Etanercept 3 arofylline & CytoFAb & PassTNF 6 arofylline & CDP-870 7 arofylline & beclomethasone 8 arofylline & be arofylline & deflazacort 11 arofylline & flunisolide 12 arofylline & fluticasone 13 ar onercept 15 arofylline & pentoxifylline 16 arofylline & thalidomide 17 arofylline & triamcinolone 19 arofylline & ciclesonide 20 arofylline & Pegsunercept 21 atizoran Etanercept 23 atizoram & CytoFAb 24 atizoram & Afelimomab 25 atizoram & Pass atizoram & beclomethasone 28 atizoram & beconase 29 atizoram & budesonide 3 & flunisolide 32 atizoram & fluticasone 33 atizoram & ketotifen 34 atizoram & one atizoram & thalidomide 37 atizoram & prednisone 38 atizoram & triamcinolone 3S Pegsunercept 41 AWD-12-281 & Infliximab 42 AWD-12-281 & Etanercept 43 AWI & Afelimomab 45 AWD-12-281 & PassTNF 46 AWD-12-281 & CDP-870 47 AWD-1 281 & beconase 49 AWD-12-281 & budesonide 50 AWD-12-281 & deflazacort 51 12-281 & fluticasone 53 AWD-12-281 & ketotifen 54 AWD-12-281 & onercept 55 AWD-12-281 & thalidomide 57 AWD-12-281 & prednisone 58 AWD-12-281 & tria ciclesonide 60 AWD-12-281 & Pegsunercept 61 bamifylline & Infliximab 62 bamif CytoFAb 64 bamifylline & Afelimomab 65 bamifylline & PassTNF 66 bamifylline & beclomethasone 68 bamifylline & beconase 69 bamifylline & budesonide 70 bamif flunisolide 72 bamifylline & fluticasone 73 bamifylline & ketotifen 74 bamifylline & pentoxifylline 76 bamifylline & thalidomide 77 bamifylline & prednisone 78 bamify ciclesonide 80 bamifylline & Pegsunercept 81 CDC-801 & Infliximab 82 CDC-801

84 CDC-801 & Afelimomab 85 CDC-801 & PassTNF 86 CDC-801 & CDP-870 87 CD & beconase 89 CDC-801 & budesonide 90 CDC-801 & deflazacort 91 CDC-801 & f 93 CDC-801 & ketotifen 94 CDC-801 & onercept 95 CDC-801 & pentoxifylline 96 prednisone 98 CDC-801 & triamcinolone 99 CDC-801 & ciclesonide 100 CDC-801 Infliximab 102 CDP 840 & Etanercept 103 CDP 840 & CytoFAb 104 CDP 840 & Afe CDP 840 & CDP-870 107 CDP 840 & beclomethasone 108 CDP 840 & beconase 1(840 & deflazacort 111 CDP 840 & flunisolide 112 CDP 840 & fluticasone 113 CDP onercept 115 CDP 840 & pentoxifylline 116 CDP 840 & thalidomide 117 CDP 840 triamcinolone 119 CDP 840 & ciclesonide 120 CDP 840 & Pegsunercept 121 cilom Etanercept 123 cilomilast & CytoFAb 124 cilomilast & Afelimomab 125 cilomilast & 127 cilomilast & beclomethasone 128 cilomilast & beconase 129 cilomilast & bude 131 cilomilast & flunisolide 132 cilomilast & fluticasone 133 cilomilast & ketotifen cilomilast & pentoxifylline 136 cilomilast & thalidomide 137 cilomilast & prednison cilomilast & ciclesonide 140 cilomilast & Pegsunercept 141 cipamfylline & Infliximi cipamfylline & CytoFAb 144 cipamfylline & Afelimomab 145 cipamfylline & PassTN cipamfylline & beclomethasone 148 cipamfylline & beconase 149 cipamfylline & bi deflazacort 151 cipamfylline & flunisolide 152 cipamfylline & fluticasone 153 cipar onercept 155 cipamfylline & pentoxifylline 156 cipamfylline & thalidomide 157 cip cipamfylline & triamcinolone 159 cipamfylline & ciclesonide 160 cipamfylline & Pe 162 D-4418 & Etanercept 163 D-4418 & CytoFAb 164 D-4418 & Afelimomab 165 CDP-870 167 D-4418 & beclomethasone 168 D-4418 & beconase 169 D-4418 & t 171 D-4418 & flunisolide 172 D-4418 & fluticasone 173 D-4418 & ketotifen 174 D pentoxifylline 176 D-4418 & thalidomide 177 D-4418 & prednisone 178 D-4418 & ciclesonide 180 D-4418 & Pegsunercept 181 doxofylline & Infliximab 182 doxofyll CytoFAb 184 doxofylline & Afelimomab 185 doxofylline & PassTNF 186 doxofylline beclomethasone 188 doxofylline & beconase 189 doxofylline & budesonide 190 dc & flunisolide 192 doxofylline & fluticasone 193 doxofylline & ketotifen 194 doxofyl pentoxifylline 196 doxofylline & thalidomide 197 doxofylline & prednisone 198 do doxofylline & ciclesonide 200 doxofylline & Pegsunercept 201 dyphylline & Inflixin dyphylline & CytoFAb 204 dyphylline & Afelimomab 205 dyphylline & PassTNF 20 & beclomethasone 208 dyphylline & beconase 209 dyphylline & budesonide 210 d & flunisolide 212 dyphylline & fluticasone 213 dyphylline & ketotifen 214 dyphyllir pentoxifylline 216 dyphylline & thalidomide 217 dyphylline & prednisone 218 dypl & ciclesonide 220 dyphylline & Pegsunercept 221 ibudilast & Infliximab 222 ibudil CytoFAb 224 ibudilast & Afelimomab 225 ibudilast & PassTNF 226 ibudilast & CDP 228 ibudilast & beconase 229 ibudilast & budesonide 230 ibudilast & deflazacort & fluticasone 233 ibudilast & ketotifen 234 ibudilast & onercept 235 ibudilast & pe thalidomide 237 ibudilast & prednisone 238 ibudilast & triamcinolone 239 ibudilas Pegsunercept 241 KW 4490 & Infliximab 242 KW 4490 & Etanercept 243 KW 449

244 KW 4490 & Afelimomab 245 KW 4490 & PassTNF 246 KW 4490 & CDP-870 2 KW 4490 & beconase 249 KW 4490 & budesonide 250 KW 4490 & deflazacort 25 & fluticasone 253 KW 4490 & ketotifen 254 KW 4490 & onercept 255 KW 4490 & thalidomide 257 KW 4490 & prednisone 258 KW 4490 & triamcinolone 259 KW 4 Pegsunercept 261 L-791943 & Infliximab 262 L-791943 & Etanercept 263 L-7919 Afelimomab 265 L-791943 & PassTNF 266 L-791943 & CDP-870 267 L-791943 & beconase 269 L-791943 & budesonide 270 L-791943 & deflazacort 271 L-791943 fluticasone 273 L-791943 & ketotifen 274 L-791943 & onercept 275 L-791943 & thalidomide 277 L-791943 & prednisone 278 L-791943 & triamcinolone 279 L-79 Pegsunercept 281 lirimilast & Infliximab 282 lirimilast & Etanercept 283 lirimilast 285 lirimilast & PassTNF 286 lirimilast & CDP-870 287 lirimilast & beclomethasone lirimilast & budesonide 290 lirimilast & deflazacort 291 lirimilast & flunisolide 292 ketotifen 294 lirimilast & onercept 295 lirimilast & pentoxifylline 296 lirimilast & t 298 lirimilast & triamcinolone 299 lirimilast & ciclesonide 300 lirimilast & Pegsune ONO-6126 & Etanercept 303 ONO-6126 & CytoFAb 304 ONO-6126 & Afelimomab 6126 & CDP-870 307 ONO-6126 & beclomethasone 308 ONO-6126 & beconase 3 6126 & deflazacort 311 ONO-6126 & flunisolide 312 ONO-6126 & fluticasone 313 & onercept 315 ONO-6126 & pentoxifylline 316 ONO-6126 & thalidomide 317 ON & triamcinolone 319 ONO-6126 & ciclesonide 320 ONO-6126 & Pegsunercept 321 189659 & Etanercept 323 PD-189659 & CytoFAb 324 PD-189659 & Afelimomab 3 189659 & CDP-870 327 PD-189659 & beclomethasone 328 PD-189659 & beconas PD-189659 & deflazacort 331 PD-189659 & flunisolide 332 PD-189659 & fluticaso PD-189659 & onercept 335 PD-189659 & pentoxifylline 336 PD-189659 & thalido 338 PD-189659 & triamcinolone 339 PD-189659 & ciclesonide 340 PD-189659 & Infliximab 342 pentoxifylline & Etanercept 343 pentoxifylline & CytoFAb 344 pent pentoxifylline & PassTNF 346 pentoxifylline & CDP-870 347 pentoxifylline & beclo

beconase 349 pentoxifylline & budesonide 350 pentoxifylline & deflazacort 351 pe pentoxifylline & fluticasone 353 pentoxifylline & ketotifen 354 pentoxifylline & one 356 pentoxifylline & prednisone 357 pentoxifylline & triamcinolone 358 pentoxifyl Pegsunercept 360 piclamilast & Infliximab 361 piclamilast & Etanercept 362 piclai Afelimomab 364 piclamilast & PassTNF 365 piclamilast & CDP-870 366 piclamilast beconase 368 piclamilast & budesonide 369 piclamilast & deflazacort 370 piclamil fluticasone 372 piclamilast & ketotifen 373 piclamilast & onercept 374 piclamilast thalidomide 376 piclamilast & prednisone 377 piclamilast & triamcinolone 378 pic & Pegsunercept 380 pumafentrin & Infliximab 381 pumafentrin & Etanercept 382 pumafentrin & Afelimomab 384 pumafentrin & PassTNF 385 pumafentrin & CDP-8 beclomethasone 387 pumafentrin & beconase 388 pumafentrin & budesonide 389 pumafentrin & flunisolide 391 pumafentrin & fluticasone 392 pumafentrin & ketoti pumafentrin & pentoxifylline 395 pumafentrin & thalidomide 396 pumafentrin & p triamcinolone 398 pumafentrin & ciclesonide 399 pumafentrin & Pegsunercept 40 roflumilast & Etanercept 402 roflumilast & CytoFAb 403 roflumilast & Afelimomab roflumilast & CDP-870 406 roflumilast & beclomethasone 407 roflumilast & becon roflumilast & deflazacort 410 roflumilast & flunisolide 411 roflumilast & fluticason roflumilast & onercept 414 roflumilast & pentoxifylline 415 roflumilast & thalidom roflumilast & triamcinolone 418 roflumilast & ciclesonide 419 roflumilast & Pegsur rolipram & Etanercept 422 rolipram & CytoFAb 423 rolipram & Afelimomab 424 rc CDP-870 426 rolipram & beclomethasone 427 rolipram & beconase 428 rolipram deflazacort 430 rolipram & flunisolide 431 rolipram & fluticasone 432 rolipram & rolipram & pentoxifylline 435 rolipram & thalidomide 436 rolipram & prednisone 4 rolipram & ciclesonide 439 rolipram & Pegsunercept 440 SCH-351591 & Infliximal SCH-351591 & CytoFAb 443 SCH-351591 & Afelimomab 444 SCH-351591 & Pass SCH-351591 & beclomethasone 447 SCH-351591 & beconase 448 SCH-351591 & deflazacort 450 SCH-351591 & flunisolide 451 SCH-351591 & fluticasone 452 SCI 351591 & onercept 454 SCH-351591 & pentoxifylline 455 SCH-351591 & thalidor 457 SCH-351591 & triamcinolone 458 SCH-351591 & ciclesonide 459 SCH-35159 Infliximab 461 T-440 & Etanercept 462 T-440 & CytoFAb 463 T-440 & Afelimoma CDP-870 466 T-440 & beclomethasone 467 T-440 & beconase 468 T-440 & budes 440 & flunisolide 471 T-440 & fluticasone 472 T-440 & ketotifen 473 T-440 & one T-440 & thalidomide 476 T-440 & prednisone 477 T-440 & triamcinolone 478 T-4 Pegsunercept 480 Theophylline & Infliximab 481 Theophylline & Etanercept 482 T Theophylline & Afelimomab 484 Theophylline & PassTNF 485 Theophylline & CDP- beclomethasone 487 Theophylline & beconase 488 Theophylline & budesonide 48 Theophylline & flunisolide 491 Theophylline & fluticasone 492 Theophylline & keto Theophylline & pentoxifylline

495 Theophylline & thalidomide 496 Theophylline & prednisone 497 Theophylline ciclesonide 499 Theophylline & Pegsunercept 500 V-11294A & Infliximab 501 V-1 CytoFAb 503 V-11294A & Afelimomab 504 V-11294A & PassTNF 505 V-11294A & beclomethasone 507 V-11294A & beconase 508 V-11294A & budesonide 509 V-1 flunisolide 511 V-11294A & fluticasone 512 V-11294A & ketotifen 513 V-11294A pentoxifylline 515 V-11294A & thalidomide 516 V-11294A & prednisone 517 V-11 & ciclesonide 519 V-11294A & Pegsunercept 520 YM-976 & Infliximab 521 YM-97 523 YM-976 & Afelimomab 524 YM-976 & PassTNF 525 YM-976 & CDP-870 526 Y & beconase 528 YM-976 & budesonide 529 YM-976 & deflazacort 530 YM-976 & fl 532 YM-976 & ketotifen 533 YM-976 & onercept 534 YM-976 & pentoxifylline 535 prednisone 537 YM-976 & triamcinolone 538 YM-976 & ciclesonide 539 YM-976 &

[0098] The inventionbeing thus described, it is apparent that the same can be va are not to be regarded as a departure from the spirit and scope of the present in equivalents as would be obvious to one skilled in the art are intended to be incluc clims.

<- Previous Application (Methods of using a human il-17 related po..)
beta-like molecules for treatm..) ->